

## REMARKS

In the Office Action dated November 15, 2004, the Examiner states that this application contains the following groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1. The Examiner requires Applicants to elect a single invention to which the claims must be restricted.

- |           |  |
|-----------|--|
| Group I   | Claims 1-21, drawn to a compound which interacts with the $\beta$ -amyloid peptide.  |
| Group II  | Claims 22-30, drawn to a method of selecting or designing a compound which inhibits the binding of metal ions to the N-terminus of the $\beta$ -amyloid peptide. |
| Group III | Claims 31-38, drawn to a method of inhibiting the binding of one or more metal ions to the $\beta$ -amyloid peptide.   |

The Examiner states that Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, Groups I-III lack the same or corresponding special technical features for the following reasons: claim 1 is anticipated by Shao, et al. (*J. Molecular Biol.* 285: 755-773, 1999).

The Examiner refers to Shao, page 767, where it is stated that, "[a]s for the nicotine-inhibition to  $\beta$ -amyloidosis, the NMR work established that nicotine binds to the His13 and His14 side-chains of the Tyr10-Val24  $\alpha$ -helix, and this prevented an  $\alpha$ -helix  $\rightarrow$   $\beta$ -sheet conversion and  $\beta$ -amyloid precipitation." Thus, it is Examiner's position, absent specific, substantial and credible evidence to the contrary, that binding of nicotine to  $\beta$ -amyloid protein at His13 and His14 inherently "blocks" the N-terminus in such a way that binding of metal ions at said His residues is inhibited.

According to the Examiner, the technical feature of Group I is "a compound which interacts with  $\beta$ -amyloid protein". The Examiner contends that claim 1 lacks novelty in view of

Shao and does not make a contribution over the prior art, and therefore Groups I-III cannot be unified by a special technical feature.

In order to be fully responsive to the Examiner's requirements for restriction, Applicants provisionally elect to prosecute the subject matter of Group II, claims 22-30, drawn to a method of selecting or designing a compound which inhibits the binding of metal ions to the N-terminus of the  $\beta$ -amyloid peptide. Applicants reserve the right to file one or more divisional applications to pursue the non-elected subject matter. However, Applicants hereby traverse the Examiner's requirement for restriction and request reconsideration thereof in view of the following remarks.

A requirement for restriction presupposes an analysis of the subject application in light of the rules governing this practice, i.e., 37 C.F.R. §1.499 and PCT Rules 13.1 and 13.2. PCT Rule 13.1, first sentence, states: "The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ('requirement of unity of invention')." (Emphasis added.) PCT Rule 13.2 states: "The expression 'technical features' shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art." (Emphasis added.)

Applicants respectfully submit that unity of invention is the issue at hand. Applicants should be given the opportunity to argue on the merits during prosecution as to whether the claims are novel relative to the referenced prior art. Restriction of the claims based on an allegedly anticipating reference would deny Applicants such an opportunity. Furthermore, Applicants respectfully submit that the International Search Report has not raised any issues on the basis of lack of unity of invention.

Furthermore, Applicants respectfully submit that the present application is predicated in part on the determination that zinc and copper bind predominantly to a region in the N-terminal loop of A $\beta$  that includes a cluster of histidine residues. This unique recognition provides the basis for the rational design or selection of inhibitors of the binding of zinc, copper and/or iron to A $\beta$ . It is noted that the disclosure of Shao is limited to nicotine binding to A $\beta$ . Shao does not teach or suggest design or selection of inhibitors of the binding of zinc, copper and/or iron to A $\beta$ , or any compounds made or identified on this basis. As a result of the ability to block binding by metal ions to A $\beta$ , the compounds designed or selected in accordance with the present invention are useful for treating diseases such as Alzheimer's disease. Therefore, it is respectfully submitted that all claims presented in the pending application are directed to the design, making and use of compounds that inhibit the binding of metal ions to A $\beta$  at identified residues or regions of A $\beta$ , thereby inhibiting the aggregation of A $\beta$ , which is useful for treating conditions such as Alzheimer's disease. It is submitted that the present claims are so linked as to form a single general inventive concept, and should be examined in the same application. At the very least, Applicants respectfully submit that Group II, drawn to methods of design and selection of relevant compounds, and Group III, drawn to therapeutic methods by employing the relevant compounds, should be examined together.

Applicants further respectfully submit that the Examiner has not included claims 39-44 in the Restriction Requirement. In this regard, claims 39-42 were included when the application was initially filed as an international application (PCT/AU00/00886). Claims 43-44 were added in the Preliminary Amendment mailed on January 18, 2002. Claims 3, 6-7, 11, 15, 19, 21, 25-27, 29-30 and 35-41 were also amended by way of the Preliminary Amendment. A courtesy copy of the Preliminary Amendment mailed on January 18, 2002 is enclosed.

Applicants respectfully submit that claims 39-41 and 44 are directed to therapeutic methods by employing the relevant compounds. Claim 43 is directed to a pharmaceutical composition comprising a compound obtained or selected in accordance with the present invention. It is requested that claims 39-44 be examined with the elected claims.

Finally, Applicants respectfully submit that a determination to make the pending restriction requirement final must evidence the patentable distinctness of all defined three groups, one from the other, as presented by the Examiner.

Accordingly, it is respectfully submitted that the present application satisfies the requirements for unity of invention. Applicants respectfully urge that the Examiner reconsider and withdraw the requirement for restriction and provide an action on the merits with respect to all the claims.

Respectfully submitted,



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Enc.: copy of the Preliminary Amendment mailed on January 18, 2002.



PATENTS

Attorney Docket No. 113122.120

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
(DO/EO/US)

Applicant: Barnham *et al.*

Serial No.: Unassigned

Filing Date: Herewith

Title: Beta-Amyloid Peptide Inhibitors

Art Unit: Unassigned

Examiner: Unassigned

**BOX PCT**

Assistant Commissioner for Patents  
Washington, DC 20231

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1/18/02  
Date of signature and  
of mail deposit

Sharon Matthews  
Sharon Matthews

PRELIMINARY AMENDMENT

Dear Sir:

Prior to the substantive examination of the above-identified application, kindly amend the application as follows:

Amendments to the Specification:

Please add the following Abstract after page 45 of the Specification:

ABSTRACT

The present invention relates to compounds which inhibit the binding of metal ions to a region in the N-terminal loop of the  $\beta$ -amyloid peptide which includes a cluster of histidine residues. In addition, the invention relates to pharmaceutical

compositions including these compounds as the active agent, and to methods of treatment involving the administration of these compounds. The compounds of the invention are useful in the treatment of Alzheimer's Disease and other amyloid-related conditions. In a first aspect the present invention provides a compound which interacts with the  $\beta$ -amyloid peptide in such a way that the N-terminal loop of the peptide (amino acid residues 1-15) is blocked or destabilised, thereby inhibiting the binding of one or more metal ions to at least one histidine residue within the N-terminal loop. Preferably the compound inhibits binding of  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  ions, but not  $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$  ions.

#### Amendments to the Claims:

Please amend claims 3, 6-7, 11, 15, 19, 21, 25-27, 29-30, and 35-41, and add new claims 43-44 as follows. A clean version of the amended claims and the new claims is submitted in accordance with 37 C.F.R. § 1.121(c)(1)(i). A copy of the marked up amended claims in accordance with 37 C.F.R. § 1.121(c)(1)(ii) and a clean version of the entire set of pending claims in accordance with 37 C.F.R. § 1.121(c)(3) are attached hereto.

3. (Amended) A compound according to claim 1 which has a conformation and polarity such that it binds to at least one histidine residue in the N-terminal loop, selected from the group consisting of His6, His13 and His14.
6. (Amended) A compound according to claim 1, which also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glu11.
7. (Amended) A compound according to claim 1, which has acidic groups which interact with one or more of the His residues in the N-terminal loop.
11. (Amended) A compound according to claim 1, which is an organic molecule, a peptide or a metal complex.

15. (Amended) A compound according to claim 1, which comprises, or is conjugated to, a targeting moiety, forming an inhibitor-targeting moiety complex.
19. (Amended) A compound according to claim 15, in which the targeting moiety targets the compound to a site defined by residues 15-21 of the  $\beta$ -amyloid peptide.
21. (Amended) A compound according to claim 15, in which the inhibitor-targeting moiety complex is able to penetrate the blood-brain barrier.
25. (Amended) A method according to claim 22, in which the compound also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glu1.
26. (Amended) A method according to claim 22, in which the compound inhibits binding of  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  ions, but not  $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$  ions.
27. (Amended) A method according to claim 22, in which the compound has overall hydrophobic character.
29. (Amended) A compound which inhibits the binding of metal ions to the N-terminal loop of the  $\beta$ -amyloid peptide, wherein the compound is obtained by a method according to claim 22.
30. (Amended) A composition comprising a compound according to claim 1, together with a pharmaceutically-acceptable carrier.
35. (Amended) A method according to claim 31, in which the compound also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glu1.
36. (Amended) A method according to claim 31, in which the compound inhibits binding of  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  ions, but not  $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$  ions.

37. (Amended) A method according to claim 31, in which the compound is a complex of Mn, Fe, Co, Ni, Cu, Zn, Ru, Pd, Ag, Cd, Pt, Au, Rh or Hg, with the proviso that the compound is not haemin or haematin.

38. (Amended) A method according to claim 31, in which the compound comprises, or is conjugated to, a targeting moiety.

39. (Amended) A method according to claim 38, in which the targeting moiety targets the compound to a site defined by residues 15-21 on the  $\beta$ -amyloid peptide.

40. (Amended) A method according to claim 31, in which the inhibition of binding of one or more metal ions to the  $\beta$ -amyloid peptide occurs *in vivo*.

41. (Amended) A method of prevention, treatment or alleviation of Alzheimer's disease, which method comprises the step of administering a compound according to claim 1 to a subject in need of such treatment.

43. (New) A composition comprising a compound according to claim 29, together with a pharmaceutically acceptable carrier.

44. (New) A method of prevention, treatment or alleviation of Alzheimer's disease, which method comprises the step of administering a pharmaceutical composition according to claim 30 to a subject in need of such treatment.

#### REMARKS

Upon entry of this Preliminary Amendment, claims 1-44 will be pending. The foregoing amendments to the claims were made to eliminate multiple dependency and typographical errors, and to clarify that an inhibitor-targeting moiety complex is formed in claim 15. The specification has been amended to insert after the claims the abstract that appears on the cover page of the published international application. No new matter has been introduced by these amendments. Early and favorable examination on the merits is respectfully requested.



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However, please charge any payments due or credit any overpayments to our Deposit  
Account No. 08-0219.

The Examiner is encouraged to telephone the undersigned in order to expedite  
the prosecution of the instant application.

Respectfully submitted,  
HALE AND DORR LLP

A handwritten signature in cursive script that reads "Hollie L. Baker".

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January 18, 2002

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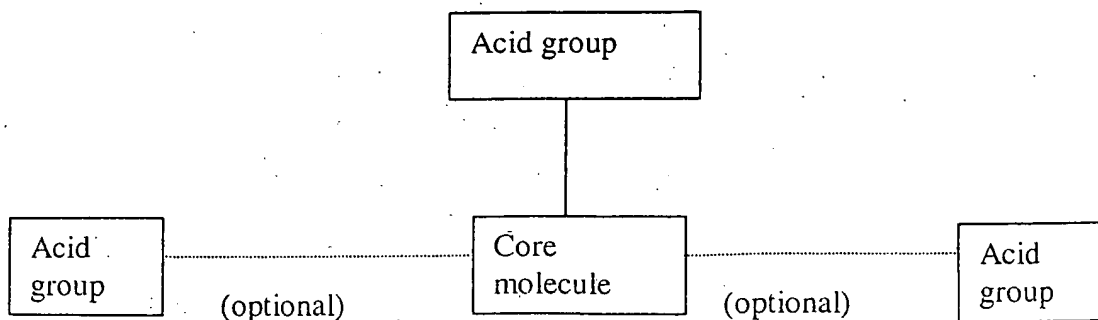
Marked Up Version of Amended Claims Under 37 C.F.R. § 1.121(c)(1)(ii)

3. (Amended) A compound according to claim 1 [or claim 2] which has a conformation and polarity such that it binds to at least one histidine residue in the N-terminal loop, selected from the group consisting of His6, His13 and His14.
6. (Amended) A compound according to [any one of] claim[s] 1 [to 5], which also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glul.
7. (Amended) A compound according to [any one of] claim[s] 1 [to 5], which has acidic groups which interact with one or more of the His residues in the N-terminal loop.
11. (Amended) A compound according to [any one of] claim[s] 1 [to 10], which is an organic molecule, a peptide or a metal complex.
15. (Amended) A compound according to [any one of] claim[s] 1 [to 14], which comprises, or is conjugated to, a targeting moiety, forming an inhibitor-targeting moiety complex.
19. (Amended) A compound according to [any one of] claim[s] 15 [to 18], in which the targeting moiety targets the compound to [the] a site defined by residues 15-21 of the  $\beta$ -amyloid peptide.
21. (Amended) A compound according to [any one of] claim[s] 15 [to 20], in which the inhibitor-targeting moiety complex is able to penetrate the blood-brain barrier.
25. (Amended) A method according to [any one of] claim[s] 22 [to 24], in which the compound also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glul.
26. (Amended) A method according to claim [26] 22, in which the compound inhibits binding of  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  ions, but not  $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$  ions.

27. (Amended) A method according to [any one of] claim[s] 22 [to 26], in which the compound has overall hydrophobic character.
29. (Amended) A compound which inhibits the binding of metal ions to the N-terminal loop of the  $\beta$ -amyloid peptide, wherein the compound is obtained by a method according to [any one of] claim[s] 22 [to 28].
30. (Amended) A composition comprising a compound according to [any one of] claim[s] 1 [to 21 or claim 29], together with a pharmaceutically-acceptable carrier.
35. (Amended) A method according to [any one of] claim[s] 31 [to 34], in which the compound also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glu11.
36. (Amended) A method according to [any one of] claim[s] 31 [to 35], in which the compound inhibits binding of  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  ions, but not  $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$  ions.
37. (Amended) A method according to [any one of] claim[s] 31 [to 36], in which the compound is a complex of Mn, Fe, Co, Ni, Cu, Zn, Ru, Pd, Ag, Cd, Pt, Au, Rh or Hg, with the proviso that the compound is not haemin or haematin.
38. (Amended) A method according to [any one of] claim[s] 31 [to 37], in which the compound comprises, or is conjugated to, a targeting moiety.
39. (Amended) A method according to claim 38, in which the targeting moiety targets the compound to [the] a site defined by residues 15-21 on the  $\beta$ -amyloid peptide.
40. (Amended) A method according to [any one of] claim[s] 31 [to 39], in which the inhibition of binding of one or more metal ions to the  $\beta$ -amyloid peptide occurs *in vivo*.
41. (Amended) A method of prevention, treatment or alleviation of Alzheimer's disease, which method comprises the step of administering a compound according to [any one of] claim[s] 1 [to 21 or a pharmaceutical composition according to claim 30] to a subject in need of such treatment.

Clean Version of Pending Claims Under 37 C.F.R. § 1.121(c)(3)

1. A compound which interacts with the  $\beta$ -amyloid peptide in such a way the N-terminal loop of the peptide (amino acid residues 1-15) is blocked or destabilised, thereby inhibiting the binding of one or more metal ions to at least one histidine residue within the N-terminal loop.
2. A compound according to claim 1 which inhibits binding  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  ions, but not  $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$  ions.
3. (Amended) A compound according to claim 1 which has a conformation and polarity such that it binds to at least one histidine residue in the N-terminal loop, selected from the group consisting of His6, His13 and His14.
4. A compound according to claim 3, which binds to at least two histidine residues in the N-terminal loop.
5. A compound according to claim 4, which binds to at least three histidine residues in the N-terminal loop.
6. (Amended) A compound according to claim 1, which also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glu11.
7. (Amended) A compound according to claim 1, which has acidic groups which interact with one or more of the His residues in the N-terminal loop.
8. A compound according to claim 7, represented as follows:



wherein the core molecule has a conformation and polarity such that the acid group(s) interact with one or more of His6, His13 and His14.

9. A compound according to claim 8, in which the acid group is selected from the group consisting of  $\text{CO}_2\text{H}$ ,  $\text{PO}_3\text{H}_2$ ,  $\text{SO}_3\text{H}$ ,  $\text{OSO}_3\text{H}_2$ , and  $\text{OPO}_3\text{H}_2$ .
10. A compound according to claim 9, which is a molecule with one to three carboxylic acid groups, the length of the molecule being such that it can be received within the N-terminal loop, and such that at least one carboxyl group is in proximity to at least one of the histidine residues.
11. (Amended) A compound according to claim 1, which is an organic molecule, a peptide or a metal complex.
12. A compound according to claim 9, which is not a metal complex.
13. A compound according to claim 9, which has overall hydrophobic character.
14. A compound according to claim 10, which is able to penetrate the blood-brain barrier.
15. (Amended) A compound according to claim 1, which comprises, or is conjugated to, a targeting moiety, forming an inhibitor-targeting moiety complex.
16. A compound according to claim 15, in which the targeting moiety is selected from the group consisting of polypeptides, nucleic acids, carbohydrates, lipids,  $\beta$ -amyloid ligands, antibodies, and dyes.
17. A compound according to claim 15, in which the targeting moiety has a hydrophobic region which interacts with the tail of the  $\beta$ -amyloid peptide.
18. A compound according to claim 17, in which the targeting moiety comprises a fatty acid molecule.

19. (Amended) A compound according to claim 15, in which the targeting moiety targets the compound to a site defined by residues 15-21 of the  $\beta$ -amyloid peptide.
20. A compound according to claim 17, in which the targeting moiety is a peptide which comprises a sequence which corresponds to that of residues 15-21 of the  $\beta$ -amyloid peptide.
21. (Amended) A compound according to claim 15, in which the inhibitor-targeting moiety complex is able to penetrate the blood-brain barrier.
22. A method of selecting or designing a compound which inhibits the binding of metal ions to the N-terminal loop of the  $\beta$ -amyloid peptide, which method comprises the steps of
- (i) selecting or designing a compound which has a conformation and polarity such that it binds to at least one amino acid in the N-terminal loop selected from the group consisting of His6, His 13 and His14; and
  - (ii) testing the compound for the ability to inhibit binding of metal ions to the N-terminal loop of the  $\beta$ -amyloid peptide.
23. A method according to claim 22, in which the compound binds to at least two histidine residues in the N-terminal loop.
24. A method according to claim 23, in which the compound binds to at least three histidine residues in the N-terminal loop.
25. (Amended) A method according to claim 22, in which the compound also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glu1.
26. (Amended) A method according to claim 22, in which the compound inhibits binding of  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  ions, but not  $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$  ions.

27. (Amended) A method according to claim 22, in which the compound has overall hydrophobic character.
28. A method according to claim 27, in which the compound is able to penetrate the blood-brain barrier.
29. (Amended) A compound which inhibits the binding of metal ions to the N-terminal loop of the  $\beta$ -amyloid peptide, wherein the compound is obtained by a method according to claim 22.
30. (Amended) A composition comprising a compound according to claim 1, together with a pharmaceutically-acceptable carrier.
31. A method of inhibiting the binding of one or more metal ions to the  $\beta$ -amyloid peptide, or of inhibiting the aggregation of  $\beta$ -amyloid peptide, which method comprises the step exposing the peptide to a compound which blocks or destabilises the N-terminal loop of the peptide, thereby inhibiting the binding of one or more metal ions to at least one histidine residue within the N-terminal loop.
32. A method according to claim 31, in which the compound has a conformation and polarity such that it binds to at least one histidine residue in the N-terminal loop of the  $\beta$ -amyloid peptide, selected from the group consisting of His6, His13 and His14.
33. A method according to claim 32, in which the compound binds to at least two histidine residues in the N-terminal loop.
34. A method according to claim 33, in which the compound binds to at least three histidine residues in the N-terminal loop.
35. (Amended) A method according to claim 31, in which the compound also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glu11.

36. (Amended) A method according to claim 31, in which the compound inhibits binding of  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  ions, but not  $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$  ions.
37. (Amended) A method according to claim 31, in which the compound is a complex of Mn, Fe, Co, Ni, Cu, Zn, Ru, Pd, Ag, Cd, Pt, Au, Rh or Hg, with the proviso that the compound is not haemin or haematin.
38. (Amended) A method according to claim 31, in which the compound comprises, or is conjugated to, a targeting moiety.
39. (Amended) A method according to claim 38, in which the targeting moiety targets the compound to a site defined by residues 15-21 on the  $\beta$ -amyloid peptide.
40. (Amended) A method according to claim 31, in which the inhibition of binding of one or more metal ions to the  $\beta$ -amyloid peptide occurs *in vivo*.
41. (Amended) A method of prevention, treatment or alleviation of Alzheimer's disease, which method comprises the step of administering a compound according to claim 1 to a subject in need of such treatment.
42. A method of prevention, treatment or alleviation of Alzheimer's disease, which method comprises inhibiting the binding of one or more metal ions to the  $\beta$ -amyloid peptide, or inhibiting the aggregation of  $\beta$ -amyloid peptide, by the method of claim 40.
43. (New) A composition comprising a compound according to claim 29, together with a pharmaceutically acceptable carrier.
44. (New) A method of prevention, treatment or alleviation of Alzheimer's disease, which method comprises the step of administering a pharmaceutical composition according to claim 30 to a subject in need of such treatment.